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(54) Implant compositions containing a biologically active protein, peptide or polypeptide.

(57) The invention relates to implant compositions for the parenteral administration of an essentially uniform and continuous amount of a biologically active protein, peptide or polypeptide over an extended period of time. The invention also relates to methods for increasing and maintaining elevated blood levels of biologically active proteins, peptides and polypeptides in animals.

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The need for and th difficulties encountered in the development of methods and compositions which continuously rel ase pharmaceutical preparations in a uniform manner ov r xtended periods of time ar well known.

The present invention relates to an implantble composition for the parenteral administration of an essentially uniform and continuous amount of a biologically active protein, peptide or polypeptide over an extended period of time which comprises a compacted, indented and partially coated composition containing from one to three layers each of which contains on a weight basis from about 20% to 80% of a biologically active protein, peptide or polypeptide, about 10% to 75% of a fat or wax or mixture thereof, 0% to about 20% of a buffer or salt or mixture thereof and 0% to about 25% of a sugar.

Surprisingly, it has been found that increased blood levels of biologically active proteins, peptides and polypeptides may be obtained and maintained for extended periods of time by implanting animals with the compacted, indented and partially coated composition of the present invention.

The implantable composition of the present invention is preferably a compacted, indented and partially coated composition containing from one to three layers each of which contains on a weight basis from about 20% to 80% of a biologically active protein, peptide or polypeptide, about 10% to 75% of a fat or wax or mixture thereof, about 1% to 20% of a buffer or salt or mixture thereof and about 1% to 25% of a sugar.

A more preferred implantable composition of this invention is a compacted, indented and partially coated composition containing from one to three layers each of which contains on a weight basis from about 35% to 70% of a biologically active protein, peptide or polypeptide, about 15% to 50% of a fat or wax or mixture thereof, about 1% to 10% of a buffer or salt or mixture thereof and about 5% to 15% of a sugar.

Biologically active proteins, peptides and polypeptides suitable for administration in the composition of the present invention include somatotropins, somatomedins, growth factor, and other biologically active fragments and derivatives thereof. Preferred proteins include porcine, ovine, equine, bovine, avian and human somatotropins; and is meant to encompass those which are of natural, synthetic, recombinant or biosynthetic origin. More preferred proteins are somatotropins with alterations in the α-helix 3 region, α-helix 2 region, combinations thereof and in combination with other mutations with E34 rpST, I122L + E34 rpST and A6TS11R + E34 rpST being most preferred.

Waxes and fats which are suitable for use in the composition of the present invention in general have melting points higher than 40°C. The wax of the invention may be defined as a low-melting organic mixture or compound of high molecular weight, solid at room temperature and generally similar in composition to fats and oils except that it contains no glycerides. Some are hydrocarbons; others are esters of fatty acids and alcohols. These compounds include saturated or unsaturated long chain C_{10}-C_{24} fatty acids, alcohols, esters, salts, ethers or mixtures thereof. They are classed among the lipids. Waxes are thermoplastic, but since they are not high polymers, they are not considered in the family of plastics. Common properties are water repellency; smooth texture; nontoxicity; freedom from objectionable odor and color. They are combustible and have good dielectric properties. They are soluble in most organic solvents and are insoluble in water.

The major types are as follows:

I. Natural
   1. Animal (beeswax, lanolin, shellac wax, Chinese insect wax)
   2. Vegetable (carnauba, candelilla, bayberry, sugarcane)
   3. Mineral
      (a) Fossil or earth waxes (ozocerite, ceresin, montan)
      (b) Petroleum waxes (paraffin, microcyrystalline slack or scale wax)

II. Synthetic
   1. Ethylenic polymers and polyol ether-esters ("Carbowax")
   2. Chlorinated naphthalenes ("Halowax")
   3. Hydrocarbon type via Fischer-Tropsch synthesis

The fat of the present invention may be defined as a glyceryl ester of higher fatty acids such as myristic, stearic and palmitic. Such esters and their mixtures are solids at room temperatures and exhibit crystalline structure. Lard and tallow are examples. There is no chemical difference betw en a fat and an oil, the only distinction being that fats are solid at room temperature and oils are liquid. The term "fat" usually refers to triglycerid s specifically, wher as "lipid" is all-inclusive.

The fat is preferably composed of mono-, di- or triglyceryl esters of long chain C_{10}-C_{24} fatty acids. The mono-, di-, or triglycerides are composed predominantly of myristates, stearates, palmitates, laurates, linoleates, linolenates, oleates, and residues or mixtures thereof, having melting points greater than 50°C,

being most preferred. Glyceryl trimyristate is a most preferred fat.

Sugars suitable for us in the composition of th present invention include mono-, di- or trisaccharid s such as glucos , mannose, sorbitol, mannitol, lactose, sucros , maltos , cellobios and raffinos . Pr ferred sugars are non-reducing mono-, di- or trisaccharid s with sucrose, raffinose, sorbitol and mannitol being most preferred.

Buffers are added to the implant compositions of the present invention to adjust the pH of the composition to a value of from about 6.0 to 8.5 in order to effect the solubility of the somatotropin and consequently the release of the somatotropin from the implant composition. Buffers suitable for use in the compositions of the invention include sodium and potassium phosphates, borates, carbonates, glycinates and the like or mixtures thereof with a mixture of monobasic sodium phosphate and dibasic sodium phosphate being preferred to adjust the pH of the compositions to a preferred value of from about 6.5 to 8.0.

Salts suitable for use in the composition of this invention include salts such as sodium chloride, potassium chloride and the like.

Additives such as stabilizers, preservatives, surfactants or mixtures thereof may be included in the compositions of the invention. Preferred stabilizers include dehydroacetic acid, salicylanilide, sorbic acid, boric acid, benzoic acid, and salts thereof; hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium nitrite and sodium nitrate. The amounts of said additives suitable for use in the invention range from about 0.1% to 20% on a weight basis.

Surprisingly, it has been found that increased blood levels of somatotropins may be obtained and maintained for extended periods of time by implanting animals with the composition of the invention. Elevated blood levels of the biologically active proteins, peptides and polypeptides are generally observed and associated with beneficial and/or therapeutic effects. The effects include weight gain, increased growth rate, improved feed efficiency, decreased body fat, improved lean meat to fat ratio, improved muscle size and increased milk production in lactating animals. Maintaining the elevated blood levels is an indication of the slow release of the active ingredient. Properties such as increased growth rate, improved feed efficiency, increased lean meat and increased milk production are generally observed when elevated blood levels of the active ingredient is maintained. The invention includes the use of the compositions herein to increase growth rate, improve feed efficiency, increase lean meat in animals, improve milk production and increase and maintain levels of somatotropins in the blood stream of animals.

Implantable composition of the present invention useful for the administration of a biologically active protein, peptide or polypeptide may be prepared by incorporating the active ingredient, buffer or salt or mixture thereof and sugar with a molten fat, wax or mixture thereof to obtain a coarse powder. Compacted and indented compositions are then prepared with a tablet press set up with conventional implant sizes such as 5/32, 1/8 inches and the like using a special top punch. The top punch has a tapered projection on the center line of the punch which will form a conical indentation in the composition when compressed. One to three layers of the coarse powder is then placed into the die and compressed with the special top punch to form compacted and indented compositions. In a preferred embodiment of the invention the amount of biologically active protein, peptide or polypeptide present in each layer increases away from the indentation. The compacted and indented compositions are then coated with one or two layers of a semipermeable material to form the implantable compositions of the invention. The indentation remains essentially uncoated and becomes a passageway for the active ingredient to exit the composition of the invention over an extended period of time.

Semipermeable materials suitable for coating the compressed and indented compositions of the present invention include semipermeable polymers such as methacrylate ester copolymers, ethyl cellulose polymers and the like. Additives such as plasticizers and fillers may be added to the semipermeable polymers in amounts of from 1% to 20% on a weight basis with triethyl citrate and talc being a preferred plasticizer and filler respectively. The thickness of each coating surrounding the compacted and indented compositions is from about 0.5 mils to 25 mils.

In order to facilitate a further understanding of the invention, the following examples are presented to illustrate more specific details thereof. The invention is not to be limited thereby except as defined in the claims.

EXAMPLE 1

Preparation of implant c mpositi ns for th parent ral administration of somatotropins

1. Preparation of somatotropin, sugar, buffer and additives in a size range suitable for incorporation in the

fat, wax or mixtur thereof by spray drying may be accomplished by dissolving the somatotropin and sugar in water and then adding the desired buffer solution such as a 1:2 mixture of monobasic and dibasic sodium phosphate. Additives such as hydroxypropyl cellulose may be added and allowed to dissolve. The solution is then spray-dried in a Buchi mini spray drier, model #190.

2. Preparation of granular powder. A homogeneous mixture of the spray dried powder in the molten fat, wax or mixture thereof is prepared and the resulting mixture is cooled to give a powder. The powder is tableted using a Stokes model #512 tablet press set up with 5/8 inch punches and dies. These tablets are milled using a benchtop Glen Mills MicrohammerMill to form a coarse granular powder.

3. Preparation of compacted and indented compositions. Layered, compacted and indented compositions are made with a Stokes model #521 single tablet press set up with a 5/32 inch die and special top punch. The top punch has a 3mm tapered projection on the center line of the punch. The base of the projection is about 1mm. To make layered, compacted and indented compositions, the inner end granular powder is placed into the die first and lightly tamped, then the indent end granular powder is placed into the die. The press is operated by hand, so that each implant is made one at a time. To make uniform implants, a 1/8 inch die and special top punch is used. The top punch has a 3 mm tapered projection on the center line of the punch and the base of the projection is about 1 mm. The desired amount of granular powder is placed into the die and the uniform, compacted and indented compositions are prepared by operating the press by hand.

4. Preparation of partially coated implant compositions. The compacted and indented compositions are coated with one or two layers of a semipermeable polymeric material using a MINI HI-COATER® (trademark of Vector Laboratories). The surface within the indentation remains essentially uncoated and becomes a passageway for the active ingredient to exit the composition of the invention over an extended period of time.

Utilizing the above procedure with the materials listed in Table I below yields the implant compositions listed in Table II below.

TABLE I

Somatotropin

a. I122L + E34 rpST

b. E34 rpST

c. A6T8I1R + E34 rpST

d. CAM - rpST

e. bovine somatotropin

Fat or Wax

f. glyceryl trimyristate

g. glyceryl tristearate

TABLE I (continued)

Sugar	
h.	sucrose
i.	lactose
Buffer	
j.	(1:2) mixture of monobasic and dibasic sodium phosphate
k.	monobasic sodium phosphate
l.	sodium borate
Additive	
m.	hydroxypropyl cellulose
Coating	
n.	poly(ethylacrylate, methylmethacrylate) (EUDRAGIT® NE30D) containing 8% by weight talc
o.	poly(ethylacrylate, methylmethacrylate) (EUDRAGIT® NE30D) containing 15% by weight talc
p.	poly(ethylacrylate, methylmethacrylate) trimethylammonioethylmethacrylate chloride (EUDRAGIT® RL30D) containing 15% by weight triethyl citrate
q.	poly(ethylacrylate, methylmethacrylate) trimethylammonioethylmethacrylate chloride (EUDRAGIT® RS30D) containing 15% by weight triethyl citrate

EUDRAGIT® is a trademark of Rohm Pharma GmbH.

TABLE II

Implant Compositions

Composition		Somato-tropin % w/w	Fat or Wax/ % w/w	Sugar/ % w/w	Buffer/ % w/w	Additive/ % w/w	Layer weight (mg)	First Coating/ mils	Second C ating/ mils
1	RE[1]	a/35.0	f/50.0	h/12.5	j/2.5	-	30	p/2	n/5
	IE[2]	a/70.0	f/17.6	h/8.2	j/4.1	-	90		
2	RE	a/35.0	f/50.0	h/12.5	j/2.5	-	50	p/2	n/5
	IE	a/70.0	f/17.6	h/8.2	j/4.1	-	80		

TABLE II (Continued)

Composition		Somato-tropin % w/w	Fat or Wax/ % w/w	Sugar/ % w/w	Buffer/ % w/w	Additive/ % w/w	Layer weight (mg)	First Coating/ mils	Second Coating/ mils
6	RE	a/40.0	f/50.0	h/7.5	j/2.5	-	50	p/2	n/5
	IE	a/65.0	f/23.5	h/7.6	j/3.8	-	80		
7	RE	a/40.0	f/20.0	h/20.0	j/4.0	m/16.0	10	p/2	n/5
	IE	a/55.0	f/31.0	h/10.3	j/3.4	-	110		
8	RE	a/40.0	f/20.0	h/20.0	j/4.0	m/16.0	20	p/2	n/5
	IE	a/55.0	f/31.3	h/10.3	j/3.4	-	100		
9	RE	a/35.0	f/30.0	h/17.5	j/3.5	m/14.0	20	p/2	n/5
	IE	a/55.0	f/31.3	h/10.3	j/3.4	-	100		
10	RE	b/40.0	f/50.0	h/7.5	j/2.5	-	50	n/5	-
	IE	b/65.0	f/18.7	h/12.2	j/4.1	-	70		

TABLE II (Continued)

Composition		Somato-tropin % w/w	Fat or Wax/ % w/w	Sugar/ % w/w	Buffer/ % w/w	Additive/ % w/w	Layer weight (mg)	First Coating/ mils	Second Coating/ mils
11	RE	b/50.0	f/37.5	h/9.4	j/3.1	-	40	q/2.5	/6
	IE	b/60.0	f/25.0	h/11.3	j/3.8	-	80		
12	RE	c/45.0	f/43.8	h/8.4	j/2.8	-	40	p/1	n/7
	IE	c/60.0	f/25.0	h/11.3	j/3.8	-	80		
13	RE	c/50.0	f/37.5	h/9.4	j/3.1	-	40	q/2	/6
	IE	c/60.0	f/25.0	h/11.3	j/3.8	-	80		
14	Uniform	a/53.8	g/31.2	i/13.5	k/1.5	-	80	n/5	
15	Uniform	d/55.0	f/31.3	h/10.3	j/3.4	-	120	q/1	o/6.5

TABLE II (Continued)

Composition	Somatotropin % w/w	Fat or Wax/ % w/w	Sugar/ % w/w	Buffer/ % w/w	Additive/ % w/w	Layer weight (mg)	First Coating/ mils	Second Coating/ mils
16 RE	c/50.0	f/44.4	-	j/4.4 1/1.1	-	40	q/1	o/6.5
IE	c/60.0	f/33.3	-	j/5.3 1/1.3	-	90		
17 RE	e/50.0	f/37.5	h/8.8	j/2.9	-	40	q/1	o/6.5
IE	e/60.0	f/25.0	h/11.3	j/3.8	-	80		

[1] RE = Release end
[2] IE = Inner end

EXAMPLE 2

Sustained release of compositions of the invention in pigs

Pigs are divided into groups of four animals. Throughout the test, all pigs are fed the same ration

containing 20% crude protein. The pigs are not treated for thre days and daily porcin somatotropin blood levels are obtained for each group of animals. Then two implants, listed in Table II, are implanted in the ear of each pig. Somatotropin levels in the blood of the animals is determined by standard RIA techniques daily. The results of this experiment, summarized in Table III below, demonstrate the effectiveness of the compositions of the invention for increasing and maintaining elevated somatotropin levels in the blood for extended periods of time.

TABLE III

Average Plasma rpST Concentration (ng/mL by Radioimmunoassay) for Pig Experiments						
Time (Days)	Composition from Table II					
	2	7	10	11	12	13
-3	1.9	1.4	1.5	2.1	3.8	2.5
-2	0.9	2.2	2.6	4.9	2.4	3.8
-1	1.2	2.3	1.7	2.4	3.3	4.2
1	6.6	5.5	4.9	1.7	3.0	1.4
2	8.2	3.5	35.2	1.5	3.5	1.6
3	9.8	13.9	97.1	2.6	3.8	3.2
4	6.3	11.3	60.9	1.9	3.2	2.4
5	3.4	17.6	56.4	1.5	18.9	8.6
6	20.1	16.2	474.8	11.2	61.2	17.6
7	26.4	20.6	242.6	3.3	40.3	22.9
8	26.1	20.0	110.6	118.1	35.4	41.3
9	50.0	19.4	70.7	87.0	19.7	43.0
10	42.9	25.9	45.4	56.6	30.0	55.0
11	26.1	35.7	82.4	44.3	15.7	32.5
12	16.0	34.2	47.1	34.8	22.7	35.3
13	26.2	29.8	52.1	40.1	6.7	25.0
14	19.9	31.4	28.8	54.4	8.0	39.8
15	10.2	25.3	21.3	25.9	4.8	20.0
16	8.8	20.7	19.7	31.3	4.7	12.5
17	13.4	10.5	6.8	29.2	4.9	10.2
18	8.0	15.4	7.8	18.5	4.0	10.0
19	32.1	34.4	10.0	16.1	3.8	5.3
20	5.8	9.4	8.2	14.9	2.8	6.8
21	9.6	13.6	9.9	8.7	2.7	3.1
22	15.1	11.2	5.7	7.4	35.6	7.1
23	60.8	7.1	6.0	15.9	12.8	4.3
24	4.9	7.6	12.6	11.2	4.0	4.4
25	8.4	7.0	5.4	5.4	2.3	3.4
26	8.9	6.6	4.0	5.3	2.7	6.8
27	6.7	7.3	4.8	8.6	5.0	6.5

EXAMPLE 3

In vitro dissolution evaluation of implants

Two implants are placed in a plastic tube containing 10 mL of a phosphate buffer solution (pH 7.4, 100 mM NaCl, 50mM Na_2HPO_4/NAH_2PO_4, 0.2% Na azide) and the tube is placed in a water bath where the temperatur of the water in the unit is maintained at 39°C. The tub is kept in the water bath for two days, then the solution is removed from the tube and analyzed for the appropriat somatotropin by HPLC and the solution is discarded. New phosphate buffer solution is add d to the tube and the tube is placed into the water bath for thre additional days and analyzed as described above. This procedure is rep ated several

times at various time intervals until the experiment is terminated. Table IV below summarizes the release rates of the appropriate somatotropin for sev ral compositions listed in Table II.

TABLE IV

Release Rate (mg/day)			
Days	Composition		
	2	7	10
0 - 2	0.6	0.6	1.0
2 - 5	3.8	7.6	11.4
5 - 9	7.2	7.0	6.9
9 - 12	5.3	3.4	4.2
12 - 16	2.7	1.7	2.1
16 - 19	1.6	1.3	1.8
19 - 23	1.3	0.9	1.4
23 - 28	0.9	0.6	1.0

Following the above procedure but analyzing the solutions for the appropriate somatotropin at different time intervals than described above gives the release rates summarized below in Tables V, VI and VII.

TABLE V

Release Rate (mg/day)		
Days	Composition	
	11	13
0 - 1	0.1	0.0
1 - 2	2.5	1.4
2 - 5	7.0	3.9
5 - 9	5.9	6.4
9 - 12	3.9	4.3
12 - 16	2.5	2.5
16 - 19	1.7	1.3
19 - 22	1.4	1.1
22 - 26	1.0	1.1
26 - 28	0.8	0.6

TABLE VI

Release Rate (mg/day)	
Days	Composition
	12
0 - 1	0.5
1 - 3	2.0
3 - 7	5.1
7 - 10	7.1
10 - 14	3.9
14 - 17	1.9
17 - 21	1.3
21 - 24	0.9
24 - 28	0.7

TABLE VII

Release Rate (mg/day)			
Days	Composition		
	15	16	17
0 - 1	0.0	0.0	0.0
1 - 2	2.2	0.7	0.7
2 - 5	1.5	3.0	3.3
5 - 9	3.9	4.4	4.5
9 - 12	4.6	4.1	2.6
12 - 16	2.4	2.3	1.1
16 - 20	1.5	1.6	0.7
20 - 23	0.9	1.2	0.4
23 - 26	0.9	1.1	0.3

Additionally, following the above procedure but using three implants gives the release rates summarized below in Table VIII.

TABLE VIII

Release Rate (mg/day)	
Days	Composition
	14
0 - 1	0.0
1 - 4	1.4
4 - 7	3.9
7 - 11	4.7
11 - 14	3.3
14 - 18	1.9
18 - 21	1.5
21 - 34	0.8

Claims

1. An implantable composition for the parenteral administration of an essentially uniform and continuous amount of a biologically active protein, peptide or polypeptide over an extended period of time characterized by a compacted, indented and partially coated composition containing from one to three layers each of which contains on a weight basis from about 20% to 80% of a biologically active protein, peptide or polypeptide, about 10% to 75% of a fat or wax or mixture thereof, 0% to about 20% of a buffer or salt or mixture thereof and 0% to about 25% of a sugar.

2. The composition according to claim 1 wherein the biologically active protein, peptide or polypeptide is selected from the group consisting of somatotropins, somatomedins, and growth factors, including porcine, ovine, equine, bovine, avian and human somatotropins; the fat is selected from the group consisting of glyceryl trimyristate, glyceryl tripalmitate and glyceryl tristearate, the buffer is selected from the group consisting of sodium borate, sodium carbonate, monobasic sodium phosphate, dibasic sodium phosphate and mixtures thereof, the sugar is selected from the group consisting of glucose, mannose, sucrose, raffinose, sorbitol, mannitol and lactose; the coating comprises one or two layers of a semipermeable material and wherein said composition optionally is characterized by a stabilizer, a surfactant or mixtures thereof.

3. The composition according to claim 2 wherein the porcine somatotropin is selected from the group consisting of E34 rpST, I122L + E34 rpST and A6TS11R + E34 rpST.

4. The composition according to claim 2 wherein the buffer is a mixture of monobasic sodium phosphate and dibasic sodium phosphate.

5. The composition according to claim 2 wherein the semipermeable material is a methacrylate ester copolymer containing on a weight basis from about 1% to 20% ethyl citrate or talc and the thickness of each coating is from about 0.5 mils to 25 mils.

6. The composition according to claim 1 wherein the amount of biologically active protein, peptide or polypeptide present in each layer increases away from the indentation.

7. A method for elevating and maintaining elevated blood levels of a biologically active protein, peptide or polypeptide, increasing growth rate, improving feed efficiency, improving loan meat to fat ratio and increasing milk production in lactating animals characterized by parenterally administering to the animal an implantable composition as characterized by claim 1.

8. The method according to claim 7 wherein the implantable composition is as characterized by claim 2.

9. A process for the preparation of an implantable composition for the parenteral administration of an essentially uniform and continuous amount of a biologically active protein, peptide or polypeptide over an extended period of time characterized by:
   (a) mixing the biologically active protein, peptide or polypeptide with a molten fat, wax or mixture thereof and optionally with a buffer, salt or sugar to form a coarse powder;
   (b) compacting one to three layers of the coarse powder to form a compacted mass;
   (c) punching the compacted mass with a tapered projection to form a tapered indentation in the compacted mass; and
   (d) coating the indented compacted mass with a semipermeable material such that a passageway is formed by the indentation from the compacted mass through the coating.

10. The process according to claim 9 wherein step (b) and step (c) occur simultaneously.

11. The process according to claim 9 wherein the compacted mass is characterized by the composition of claim 1.

12. The process according to claim 9 wherein step (a) is further characterized by:
   (a) dissolving the biologically active protein, peptide or polypeptide, and buffer or salt or mixture thereof, in water to form a solution;
   (b) spray drying the solution to form a spray dried powder;
   (c) dissolving the spray dried powder in the molten fat, wax or mixture thereof to form a

homogen ous mixture;
(d) cooling the homogeneous mixtur to form a powder;
(e) compr ssing the powder to form a compr ssed mass; and
(f) milling the compressed mass to form a coars granular powder.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 10 7278

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
P,X P,Y	WO-A-9 202 211 (ENDOCON INC.) * claims 1,6-8 * * page 13, line 12 - line 18 * * page 14, line 5 - line 25 *	1 2,5,7,8	A61K9/00
Y	EP-A-0 246 540 (WANG, PAUL Y.) * claims 1,3-10 * * examples 2,3 *	2,7,8	
Y	EP-A-0 403 032 (MONSANTO COMPANY) * claims 1,7 * * page 2, line 26 - line 31 * * page 6, line 36 - line 44 * * page 6, line 54 - line 57 *	5	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	12 OCTOBER 1992	VENTURA AMAT A.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
: non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)